ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, July 2001, p. 2183–2184 Vol. 45, No. 7
0066-4804/01/$04.00+0 DOI: 10.1128/AAC.45.7.2183–2184.2001

Levofloxacin-Resistant *Streptococcus pneumoniae*: Second Look

Jorgensen et al. have recently reported on the activities of four quinolones against a selected group of *Streptococcus pneumoniae* isolates resistant to levofloxacin (3). This report raised several important issues regarding the current status of quinolone resistance among pneumococci. Specific issues include, first, the current prevalence of fluoroquinolone resistance among pneumococci and, second, whether some fluoroquinolones can serve as therapeutic alternatives for infections caused by strains resistant to other fluoroquinolones.

Although Jorgensen et al. correctly state that quinolone resistance in *S. pneumoniae* has been described, it is important to note that recent studies have clearly established that this resistance continues to be a rare occurrence (2, 5, 7, 8; L. J. Selman, D. C. Mayfield, C. Thornsberry, Y. R. Mauriz, and D. F. Sahm, Abstr. 40th Intersci. Conf. Antimicrob. Agents Chemother., abstr. 1800, p. 111, 2000). For example, among 17,943 isolates of *S. pneumoniae* collected from more than 200 institutions per year (from 1997 to 2000) as part of the TRUST surveillance initiative, only 83 levofloxacin-resistant isolates (0.5%) and 20 levofloxacin- and penicillin-resistant isolates (0.1%) were encountered (Selman et al. 40th ICAAC). In addition, Chen et al. reported that only 0.3% of their pneumococcal isolates (25 of 7,551) were resistant to levofloxacin (1).

Chen et al. also reported that ciprofloxacin resistance had increased in their study population, but that has also raised some questions. For example, in one study the rate of ciprofloxacin nonsusceptibility among 5,640 recent clinical isolates from across the United States was only 0.3% (i.e., ciprofloxacin MICs were $\geq$4 μg/ml), and the current ciprofloxacin MIC distributions were essentially unchanged from those reported at the time ciprofloxacin became available for clinical use in the United States in the 1980s (6). Also of interest is a recent report from Japan in which levofloxacin resistance in *S. pneumoniae* isolates was <1% even though levofloxacin has been used extensively in Japan since the early 1990s (8). Clearly, the preponderance of current research suggests that current levels of pneumococcal resistance to currently available fluoroquinolones remain quite low (1, 2, 4, 5; Selman et al., 40th ICAAC), and at this time there seems to be very little if any clear association between fluoroquinolone use and resistance. Although regional or institutional differences may occur, e.g., the report of Chen et al., large surveillance studies yield a truer picture of the overall occurrence of resistance.

Finally, the suggestion by Jorgensen et al. that the greater potency of some quinolones could provide improved clinical efficacy against levofloxacin-resistant pneumococcal strains is premature. While it is true that some of the newer quinolones (including some not tested in this study) have lower MICs than the MIC of levofloxacin for *S. pneumoniae*, this alone does not indicate that they will be superior in treating respiratory tract infections. Such conclusions must await appropriate pharmacodynamic and clinical studies, as the authors state. This is especially important to note since mutations in the quinolone resistance-determining region of *S. pneumoniae* have resulted in decreased activities of all quinolones tested (3).

In this "era of antibiotic resistance," with all its attendant concerns, overstating resistance can have as negative an impact as understating it. Although the Jorgensen report adds yet another piece to the puzzle of fluoroquinolone resistance and its causes—particularly their evaluation of zone diameter breakpoints to detect fluoroquinolone resistance among pneumococci—each new study must be interpreted within the context of the larger picture. Local resistance data should be used to guide local therapy, but general conclusions for national or international dissemination should be based on national and international surveillance data.

REFERENCES

1. **Chen, D. K., A. McGeer, J. C. De Azavedo, and D. E. Low for the Canadian Bacterial Surveillance Network.** 1999. Decreased susceptibility of *Streptococcus pneumoniae* to fluoroquinolones in Canada. N. Engl. J. Med. **341:** 233–239.
2. **Jones, M. E., A. M. Staples, I. Critchley, C. Thornsberry, P. Heinze, H. D. Engler, and D. F. Sahm.** 2000. Benchmarking the in vitro activities of moxifloxacin and comparator agents against recent respiratory isolates from 377 medical centers throughout the United States. Antimicrob. Agents Chemother. **44:**2645–2652.
3. **Jorgensen, J. H., L. M. Weigel, J. M. Swenson, C. G. Whitney, M. J. Ferraro, and F. C. Tenover.** 2000. Activities of clinafloxacin, gatifloxacin, gemifloxacin, and trovafloxacin against recent clinical isolates of levofloxacin-resistant *Streptococcus pneumoniae*. Antimicrob. Agents Chemother. **44:**2962–2968.
4. **Peterson, D. E., and D. F. Sahm.** 1999. Fluroquinolone resistance in *Streptococcus pneumoniae*. N. Engl. J. Med. **341:**1546–1548.
5. **Sahm, D. F., M. E. Jones, M. L. Hickey, D. R. Diakun, S. V. Mani, and C. Thornsberry.** 2000. Resistance surveillance of *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* isolated in Asia and Europe, 1997–1998. J. Antimicrob. Chemother. **45:**457–466.
6. **Sahm, D. F., D. E. Peterson, I. A. Critchley, and C. Thornsberry.** 2000. Analysis of ciprofloxacin activity against *Streptococcus pneumoniae* after 10 years of use in the United States. Antimicrob. Agents Chemother. **44:**2521–2524.
7. **Thornsberry, C., P. T. Ogilvie, H. P. Holley, Jr., and D. F. Sahm.** 1999. Survey of susceptibilities of *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* isolates to 26 antimicrobial agents: a prospective U.S. study. Antimicrob. Agents Chemother. **43:**2612–2623.
8. **Yamaguchi, K., S. Miyazaki, F. Kashitani, M. Iwata, and Levofloxacin Surveillance Group.** 2000. Activities of antimicrobial agents against 5,180 clinical isolates obtained from 26 medical institutions during 1998 in Japan. Jpn. J. Antibiot. **53:**387–408.

Clyde Thornsberry
Focus Technologies, Inc.
Brentwood, Tennessee 37027

James A. Karlowsky*
Daniel F. Sahm
Focus Technologies, Inc.
13665 Dulles Technology Drive, Suite 200
Herndon, Virginia 20171

*Phone: (703) 480-2500
Fax: (703) 480-2670
E-mail: jkarlowsky@focusanswers.com

Authors' Reply

The letter by Thornsberry and colleagues has reinforced several major points in our publication, i.e., that high-level resistance to the fluoroquinolones (FQ) in pneumococci has been slow to emerge and that MICs of certain newer FQ (e.g., gatifloxacin, gemifloxacin, clinafloxacin, and trovafloxacin) are increased for levofloxacin-resistant pneumococcal strains that possess mutations in the quinolone resistance-determining regions of both *gyrA* and *parC*. We stated that it is unknown at this time whether the greater potency of the newer agents will translate into useful therapeutic activity against levofloxacin-resistant strains. However, certain other aspects of the letter require comment.

Surveillance studies have differed in the magnitude of emerging FQ resistance among pneumococcal clinical isolates. Thornsberry et al. have cited their own large surveillance studies in which the overall rate of resistance was low (i.e., ≤0.5%). However, some smaller, more focused studies (1, 5, 7) have found higher rates of diminished FQ susceptibility (i.e., 2.9 to 14.8%). Since the emergence of a resistant clone may occur first in a geographically distinct area, it is likely that regional surveillance may be the first indication of the early phase of emerging resistance. Certainly penicillin and extended-spectrum cephalosporin resistance began in specific areas and then later spread globally (2, 13). Studies have also varied with respect to the FQ tested to determine resistance rates. Two studies (1, 5) tested ciprofloxacin, a compound that has been associated with increased MICs when first-step, *parC* mutations occur (1, 11). Strains with only a single *parC* mutation often do not demonstrate phenotypic resistance to other FQ, including levofloxacin (1, 9). Mutations in both *gyrA* and *parC* generally are required for an isolate to be categorized as resistant to levofloxacin based upon NCCLS interpretive breakpoints (10). Indeed, testing of levofloxacin is an insensitive indicator of strains with emerging resistance due to single mutations. Thus, testing of ciprofloxacin may be a useful tool for recognition of first-step mutants that will form the foundation for sequential mutations that can result in high-level resistance.

Importantly, two North American studies have shown a statistically significant association between penicillin resistance and FQ resistance (1, 14). Chen et al. (1) demonstrated FQ resistance among penicillin-resistant clones (e.g., 23F, 9V, 6B, and 14) that have been associated with global dissemination of multidrug resistance (3, 4, 12). There is also some evidence that FQ use is associated with resistance. For most antibiotics, resistance is more common among isolates from children (14). FQ resistance, however, has been reported solely in isolates from adults (1), suggesting that FQ use is contributing to the emergence of these strains. It remains to be determined if genes for FQ resistance will become established in widely disseminated clones of pneumococci that currently harbor multidrug resistance factors or if self-transformation with DNA from FQ-resistant viridans group streptococci might increase resistance in pneumococci (6, 8). Surveillance studies should seek to identify first-step mutants as an early indication of future trends. In addition, because adverse outcomes can result from unrecognized resistance to FQ (15), clinical laboratories must have reliable criteria for detection of resistant strains, which was a major goal of our publication.

REFERENCES

1. **Chen, D. K., A. McGeer, J. C. de Azavedo, and D. E. Low.** 1999. Decreased susceptibility of *Streptococcus pneumoniae* to fluroquinolones in Canada. N. Engl. J. Med. **341:**233–239.
2. **Coffey, T. J., C. G. Dowson, M. Daniels, J. Zhou, C. Martin, B. G. Spratt, and J. M. Musser.** 1991. Horizontal transfer of multiple penicillin-binding protein genes, and capsular biosynthetic genes, in natural populations of *Streptococcus pneumoniae*. Mol. Microbiol. **5:**2255–2260.
3. **Enright, M. C., A. Fenoll, D. Griffiths, and B. G. Spratt.** 1999. The three major Spanish clones of penicillin-resistant *Streptococcus pneumoniae* are the most common clones recovered in recent cases of meningitis in Spain. J. Clin. Microbiol. **37:**3210–3216.
4. **Gherardi, G., C. Whitney, R. Facklam, and B. Beall.** 2000. Major related sets of antibiotic resistant pneumococci in the United States as determined by pulsed-field gel electrophoresis and pbpla-pbp2b-pbp2X-dhf restriction profiles. J. Infect. Dis. **181:**216–219.
5. **Goldsmith, C. E., J. E. Moore, and P. G. Murphy.** 1997. Pneumococcal resistance in the UK. J. Antimicrob. Chemother. **40**(Suppl. A)**:**11–18.
6. **Gonzalez, I., M. Georgiou, F. Alcaide, D. Balas, J. Linares, and A. G. DeLa Campa.** 1998. Fluoroquinolone resistance mutations in the *parC*, *parE*, and *gyrA* genes of clinical isolates of viridans group streptococci. Antimicrob. Agents Chemother. **42:**2792–2798.
7. **Ho, P.-L., T.-L. Que, D. N.-C. Tsang, T.-K. Ng, K.-H. Chow, and W.-H. Seto.** 1999. Emergence of fluoroquinolone resistance among multiply resistant strains of *Streptococcus pneumoniae* in Hong Kong. Antimicrob. Agents Chemother. **43:**1310–1313.
8. **Janoir, C., I. Podglajen, M.-D. Kitzis, C. Poyert, and L. Gutmann.** 1999. In vitro exchange of fluoroquinolone resistance determinants between *Streptococcus pneumoniae* and viridans streptococci and genomic organization of the *parE-parC* region in *S. mitis*. J. Infect. Dis. **180:**555–558.
9. **Janoir, C., V. Zeller, M.-D. Kitzis, N. J. Moreau, and L. Gutmann.** 1996. High-level fluoroquinolone resistance in *Streptococcus pneumoniae* requires mutations in *parC* and *gyrA*. Antimicrob. Agents Chemother. **40:**2760–2764.
10. **National Committee for Clinical Laboratory Standards.** 2000. Performance standards for antimicrobial susceptibility testing, tenth informational supplement. M100–S10. NCCLS, Wayne, Pa.
11. **Pan, X.-S., J. Ambler, S. Mehtar, and L. M. Fisher.** 1996. Involvement of topoisomerase IV and DNA gyrase as ciprofloxacin targets in *Streptococcus pneumoniae*. Antimicrob. Agents Chemother. **40:**2321–2326.
12. **Sa-Leao, R., A. Tomaz, I. Santo Sanches, A. Brito-Avo, S. E. Vilhelmsson, K. G. Kristensson, and H. de Lancastre.** 2000. Carriage of internationally spread clones of *Streptococcus pneumoniae* with unusual drug resistance patterns in children attending day care centers in Lisbon, Portugal. J. Infect. Dis. **182:**1153–1160.
13. **Tomasz, A.** 1997. Antibiotic resistance in *Streptococcus pneumoniae*. Clin. Infect. Dis. **24:**S85–S88.
14. **Whitney, C. G., M. M. Farley, J. Hadler, L. H. Harrison, C. Lexau, A. Reingold, L. Lefkowitz, P. R. Cieslak, M. Cetron, E. R. Zell, J. H. Jorgensen, and A. Schuchat.** 2000. Increasing prevalence of multidrug-resistant *Streptococcus pneumoniae* in the United States. N. Engl. J. Med. **343:**1917–1924.
15. **Wortmann, G. W., and S. P. Bennett.** 1999. Fatal meningitis due to levofloxacin-resistant *Streptococcus pneumoniae*. Clin. Infect. Dis. **29:**1599–1600.

James H. Jorgensen*
Department of Pathology
University of Texas Health Science Center
7703 Floyd Curl Drive
San Antonio, Texas 78284-7750

L. M. Weigel
J. M. Swenson
C. G. Whitney
F. C. Tenover
Centers for Disease Control and Prevention
Atlanta, Georgia 30333

M. J. Ferraro
Massachusetts General Hospital
Boston, Massachusetts 02114

*Phone: (210) 567-4088
Fax: (210) 567-2367
E-mail: jorgensen@uthscsa.edu